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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/735,180

12/12/2003

Larry Norton

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EXAMINER

OLSON, ERIC

ART UNIT

PAPER NUMBER

1623

NOTIFICATION DATE

DELIVERY MODE

06/23/2008

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/735,180	Applicant(s) NORTON, LARRY	
	Examiner Eric S. Olson	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 40-43,45-69,71-82,119-125 and 129-138 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40-43,45-69,71-82,119-125 and 129-138 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2008 has been entered.

This office action is a response to applicant's amendment and arguments submitted March 12, 2008 wherein claim 119 is amended, claims 126-128 are cancelled, and new claims 129-138 are introduced. This application claims benefit of provisional application 60/432840, filed December 12, 2002.

Claims 40-43, 45-69, 71-82, 119-125, and 129-138 are pending in this application.

Claims 40-43, 45-69, 71-82, 119-125, and 129-138 as amended are examined on the merits herein.

The following rejections of record in the previous office action are maintained:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 40-43, 45-69, 71-82, and 119-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudis et. al. '99 (Reference of record in previous office action, titled "Sequential Dose-Dense Doxorubicin, Paclitaxel, and Cyclophosphamide for Resectable High-Risk Breast Cancer :Feasibility and Efficacy", Journal of Clinical oncology (1999) Vol. 17, No. 1, pp. 93-100), in view of Henderson et al. (reference of record in previous office action) in view of Winer et al. (Reference of record in previous action)

Hudis et. al. '99 describes a course of sequential dose-dense chemotherapy using the same three drugs specified by the claimed invention. In particular, p. 95, Fig. 1 illustrates the course of treatment used, which consisted of three doses of Doxorubicin, separated by 2 weeks (14 days) each, three doses of Paclitaxel separated by 2 weeks each, and three doses of cyclophosphamide separated by 2 weeks each. The same course of treatment is described on p. 94 right column, under the heading *Treatment Plan*. Furthermore, the same paragraph mentioned above (p. 94, left column, *Treatment Plan*.) also discloses that, "All nine cycles of chemotherapy were supported by granulocyte colony stimulating factor, 5 µg/kg subcutaneously, administered on days 3 through 10." Hudis et al. '99 discusses the strategy of dose escalation and determines that dose densification is a superior strategy to dose escalation for improving the effectiveness of chemotherapy. (p. 94, left column, paragraphs 3-4) In addition, Hudis et al. discusses the relatively high doses of the drugs used and concludes that there is no evidence that the doses used were actually

superior to lower doses of 60, 600, and 175 mg/m² for doxorubicin, cyclophosphamide, and paclitaxel, respectively. (p. 97, paragraph 2 – p. 98, paragraph 1) Hudis et al. '99 does not teach the specific doses of 60, 175, and 600 mg/m² for doxorubicin, paclitaxel, and cyclophosphamide mentioned in the aforementioned claims, nor does Hudis et. al. teach the administration of said chemotherapy agents in four cycles or in an order other than doxorubicin first, paclitaxel second, and cyclophosphamide third.

Henderson et al. describes a study (CALGB 9344) comparing several chemotherapy regimens involving Doxorubicin, Paclitaxel, and Cyclophosphamide. These drugs were administered in amounts of 60, 75, and 600 mg/m² in four cycles each. Furthermore, the study concluded that escalation of the dose of doxorubicin produced no additional benefit.

Winer et al. discloses a study of dose intensification of paclitaxel. Doses of 175, 210, and 250 mg/m² were compared and it was determined that the higher doses showed no improvement in response or survival over 175 mg/m². Although the time to progression was longer, this benefit was offset by the greater toxicity at the higher doses.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Hudis et. al. '99 by reducing the dosage of the drugs used and increasing the number of cycles in each treatment, as well as by administering the three drugs in the various orders disclosed in instant claims 120-125.

One of ordinary skill in the art would have been motivated to do so in order to avoid administering an excess of these toxic drugs by reducing the dose and to ensure

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complete eradication of cancer cells by adding a fourth cycle to each treatment, particularly in view of the teaching of Henderson et al. and Winer et al. disclosing that lower doses of these drugs are equally effective. One of ordinary skill in the art would have been motivated to administer the drugs in a different order because the neither Hudis et al. '99 nor any other prior art discloses any reason to believe that the order in which the drugs are administered in a dose-dense regimen affects the treatment outcome. In particular, because the different drugs are considered to act on different selectively sensitive sub-populations, it should not matter which sub-population is eradicated first by the chemotherapy regimen as each sub-population is only significantly affected by one particular phase of the sequential treatment.

One of ordinary skill in the art would have reasonably expected success because the reduced doses and increased number of cycles were already known to be effective for the treatment of breast cancer, and because the treatment regimen of the instant invention differs only slightly from that of Hudis et al. '99. Furthermore, determination of exact treatment regimens, including exact dosage, duration of treatment, and order of administration of various drugs, is within the ordinary skill in the practice of medicine.

Although Henderson et al. and Winer et al disclose a non-dose-dense protocol, the specific dosages used by these references can be applied to a dose-dense protocol with a reasonable expectation of success because the differences observed between dose-dense and non-dose-dense protocols are not the result of any changes in the dose-response curve of the drugs used but rather the result of the same drug, producing the same cell kill percentage, being used more often. In fact, the theoretical

rationale for dose-dense chemotherapy, disclosed on p. 93, left column, second paragraph of Hudis et al. '99, rests on the knowledge that, "In these laboratory models, anticancer drugs kill a fraction of cells (called log-kill) and this is constant regardless of the number of cells present when the drugs are administered." This statement assumes that the dose-response curve, and thus the percentage of cells killed at a given dose, does not change based on the interval between treatments. Thus the disclosure in the prior art of a particular dose of a chemotherapeutic drug used in a chemotherapy method provides a clear rationale for using the same dose in a dose-dense protocol with the expectation that the efficacy will be the same as it is in the non-dose-dense protocol.

Although Henderson et al. and Winer et al. do not examine the effect of dose escalation of cyclophosphamide on the effectiveness of these drugs, the mere fact 600 mg/m² was used with a reasonable measure of success by Henderson et al. provides a motivation and reasonable expectation of success for one of ordinary skill in the art to use this dose.

Furthermore, as stated by Applicant in the amendment submitted August 11, 2006, "the establishment of a dose-response curve, for a particular chemotherapeutic agent, against a particular cancer, is part of the **routine experimentation** that takes place in the field of oncology," and, "the experimentation required to arrive at an optimal dose, for a particular chemotherapeutic agent, against a particular cancer, is **absolutely routine** in the field of oncology." Even assuming, for the sake of argument, that Hudis et al. '99 is considered on its own merits, without the additional teaching of Henderson

et al., modifying the specific dosage levels disclosed by Hudis et al. '99 and discovering that the lower dosages disclosed in the instant claims are equally effective is, by Applicant's own reasoning, merely routine and ordinary experimentation which is therefore obvious over the prior art. Therefore, although Henderson et al. has been cited to demonstrate that lower doses of the disclosed chemotherapeutic agents were known in the art at the time of the invention, Henderson et al. is not necessary to repair the defect in the teaching of Hudis et al. '99 and render the instant claims obvious.

Therefore the invention taken as a whole is prima facie obvious.

Response to Argument: Applicant's arguments submitted March 12, 2008 have been fully considered as applied to the above rejection and have not been found to be persuasive to overcome the rejection of the instant claims under 35 USC 103.

Applicant asserts that the references teach away from their combination. Specifically, it is claimed that the Hudis et al. '99 reference discloses that there "may be a small additional benefit" to using doses of paclitaxel over 175 mg/m^2 , and that the high doses used in the disclosed study were chosen because there was no confirmation that lower doses would be equivalent to higher doses. These observations do not teach or suggest that lower doses are inferior, but merely that the authors of the Hudis et al. '99 reference did not know whether or not they were equivalent. This is not a "teaching away" so much as a "failure to teach toward" the claimed invention. The uncertain, equivocal teachings of Hudis et al. '99 (which was concerned with dosage frequency and sequence, not dose intensity) as regards the optimal dose intensity would not lead one of ordinary skill in the art away from the clear teachings of Henderson and Winer,

which are in fact concerned with finding the optimal dose intensity. One of ordinary skill in the art would not see the teaching of Hudis et al. '99 as a positive recommendation of a high dose of chemotherapy agents but as a failure to recommend any specific dose intensity.

Applicant further argues that Winer et al., which was an earlier clinical trial that would have been considered by the authors of Hudis et al. when choosing dosage levels, teaches that higher doses of paclitaxel increase time to disease progression. However, the same reference teaches that despite the increased time to disease progression there is no increase in survival or quality of life for increased doses. In other words, the toxicity of higher doses leads to increased morbidity and mortality that cancels out whatever benefit is gained from the increased time to progression. Fully 19% of patients receiving 250 mg/m² of paclitaxel discontinued therapy due to toxicity. Although some patients may survive longer on this dose, others are killed by the therapy itself, as indicated by the fact that survival is not increased with increasing dose even in the face of increased time to disease progression. Therefore one of ordinary skill in the art would see that the choice of dosage is a trade-off between disease-related mortality and morbidity on one hand, and drug-related mortality and morbidity on the other. No chemotherapeutic regimen is without risk, and administering these drugs is not without risk. In many cases the lower dosage would be appropriate, as administering the higher dose would not actually be expected to improve the patients' survival or quality of life.

Applicant cites *Tec Air, Inc. v. Denson MFG. Michigan Inc* to argue that a reference teaches away from the claims when a person of ordinary skill “would be led in a direction divergent from the path that was taken by the applicant.” For a reference to lead one of ordinary skill in the art in a particular direction to the exclusion of other directions there must be a degree of certainty in the teaching of the reference. In the cited references Hudis et al. and Winer et al. there is no clear unequivocal teaching regarding which dose is appropriate. Hudis et al. and Winer et al. do not lead one of ordinary skill in the art to one specific high dosage. Rather they present a trade-off between high and low dosages, and suggest that the higher dosages may be futile in view of the lack of improved survival or quality of life. The decision of the authors of Hudis et al. to use the higher dose instead of the lower dose is not indicative of a clear teaching away from the low dose in view of the equivocation of Hudis et al. as to the benefits of dose escalation. In considering the references, one of ordinary skill in the art would have concluded that the authors of Hudis et al. were in fact uncertain as to the benefits of dose escalation and do not teach that one particular dose is superior to all others.

Therefore the rejection is deemed proper and maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
6/17/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623